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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/898,659	07/03/2001	Steven D. Tanksley	19603/3211 (CRF D-2594A)	2365

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EXAMINER

BAUM, STUART F

ART UNIT

PAPER NUMBER

1638

DATE MAILED: 05/08/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/898,659

Applicant(s)

TANKSLEY, STEVEN D.

Examiner

Stuart F. Baum

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 11 February 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,2,5-17,22-24,29-31,36-38,43-45 and 56-74 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

- 5) ☐ Claim(s) _____ is/are allowed.

- 6) ☒ Claim(s) 1,2,~~5-17~~,22-24,29-31,36-38,43-45 and 56-74 is/are rejected.

- 7) ☒ Claim(s) 5 and 6 is/are objected to.

- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on with application is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 9
- 4) ☐ Interview Summary (PTO-413) Paper No(s) _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

DETAILED ACTION

1. The amendment filed February 11, 2003 has been entered.
Claims 1-2, 5-17, 22-24, 29-31, 36-38, 43-45, and 56-74 are pending.
Claims 3-4, 18-21, 25-28, 32-35, 39-42 and 46-55 have been canceled.
Claims 1, 5-8, 36, and 43 have been amended.
2. Claims 1-2, 5-17, 22-24, 29-31, 36-38, 43-45 and 56-74 are examined in the present office action.
3. The text of those sections of Title 35, U.S. Code not included in this office action can be found in a prior office action.
4. Rejections and objections not set forth below are withdrawn.

Written Description

5. Claims 1-2, 7-8, 11-17, 22-24, 29-31, 36-38, 43-45, and 56-74 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is maintained for the reasons of record set forth in the Official action mailed 8/6/2002. Applicant's arguments filed 2/11/2003 have been fully considered but they are not persuasive.

Applicants contend that given the recited hybridization conditions and the teachings in the specification (page 4, line 20 to top of page 5; page 6, lines 6-19; and Examples 4-5), one

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skilled in the art would know what sequences are capable of hybridizing to either SEQ ID NO:1 or 3.

The Examiner disagrees that Applicants have fulfilled the written description requirements for claims drawn to sequences isolated by the stated hybridization conditions. Applicants have not specifically stated in the claim an assayable function of their claimed invention. The claims are merely drawn to a sequence that hybridizes and that increases fruit size or cell division in plants, but the precise function of their claimed invention is not disclosed. See also, MPEP § 2163 which states that the claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence. In the present application, Applicant has not specified the specific activity/function of the sequence that subsequently leads to an increase or decrease in cell division and increase or decrease in fruit size. Therefore, claiming all sequences that would hybridize to SEQ ID NO:1 or 3 under the specified hybridization conditions and exhibiting a general function of increasing fruit size or cell division does not satisfy the written description requirement.

Scope of Enablement

6. Claims 1-2, 7-17, 22-24, 29-31, 36-38, 43-45, and 56-74 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for claims limited to an isolated *Lycopersicon pennellii* ORFX gene of SEQ ID NO:1 encoding SEQ ID NO:2 and an isolated *L. esculentum* ORFX gene of SEQ ID NO:3 encoding SEQ ID NO:4 and tomato transformation therewith, to obtain tomato plants with smaller fruits as a result of less cell division does not reasonably provide enablement for claims drawn to an isolated nucleic acid molecule that hybridizes under stringent conditions characterized by a hybridization buffer comprising 0.9M sodium citrate buffer at a temperature of 45C to a nucleic acid molecule having a nucleotide sequence of SEQ ID NO:1 and plant transformation therewith to obtain reduced fruit size and/or cell division in plants, or claims drawn to an isolated nucleic acid molecule of SEQ ID NO:3 encoding SEQ ID NO:4 or to an isolated nucleic acid molecule that hybridizes under stringent conditions characterized by a hybridization buffer comprising 0.9M sodium citrate buffer at a temperature of 45C to a nucleic acid molecule having a nucleotide sequence of SEQ ID NO:3 and plant transformation therewith to obtain increased fruit size and/or cell division in plants. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicant is not enabled for the multitude of species that are claimed. Applicant's invention is isolated from tomato which is a member of the Solanaceae family, but Applicant has claimed other dicots from other plant families and has claimed plants which are monocots. The development of the tomato fruit is from the carpel (see for example Esau 1977, Anatomy of Seed

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Plants, John Wiley and Sons, New York, pages 443-444) and exhibits a very different development when compared to plants in the plant family Rosaceae (See for example Esau pages 445-448) and especially very different from monocots (see for example Esau pages 435-438). Monocots do not even have a fleshy fruit as does tomato. Given that Applicant has not demonstrated that all the claimed species possess an ORFX homologue and given that many of the claimed species exhibit a very different fruit morphology when compared to tomato, and given the lack of examples or guidance for changing the fruit morphology of the multitude of claimed species, therefore, Applicant is not enabled for claimed species found outside the Solanaceae plant family. Furthermore, the specification lacks working examples of increased fruit size or cell division. There are no examples provided for the use of any sequence in any plant species. No guidance is provided for choice of sequence, or plant species or how plants would be evaluated for these traits.

Frery et al (2000 Science 289:85-88, listed in IDS) teach that large fruited varieties of tomato (i.e., Monegrol and TA496) can be changed into producing small fruit by transforming the plants with the *fw2.2* QTL (page 85, right column, 2nd paragraph). Frery et al state "That the two complementing transformation events are independent and in different tomato lines indicates that the cos50 [*fw2.2* QTL] transgene functions similarly in different genetic backgrounds" (*supra* and page 22, paragraph 57 in specification). Frery et al also state the ORFX (which is the cloned nucleic acid molecule corresponding to the *fw2.2* QTL) transcript levels were higher in small fruited lines compared to large fruited lines (page 86, right column, 1st sentence). Frery et al conclude by stating that ORFX is a negative regulator of cell division (page 88, left column, 2nd paragraph).

Due to the unpredictable nature of transgenic plants, one of skill in the art can not reasonably know that a transformed plant will have a desired phenotype using a specific isolated gene. Levels of transgene expression in plants are generally unpredictable and vary between independent transformants; this variability is usually explained by differences in transgene copy number and/or integration site (Finnegan and McElroy, 1994. Bio/technology 12: 883-888 pg. 883 2nd paragraph, listed previously) Eshed et al (2001, Current Biology 11:1251-1260 pg 1255 2nd paragraph, listed previously) documented the phenotypes of plants transformed with the 35S CaMV promoter fused to the *KANADII* gene, which is a gene normally expressed in tissues located on the bottom side of young developing leaves. Of the 30 plants that were transformed with the *KANADII* gene, 23 plants developed only small narrow cotyledons and an arrested meristem, three produced a few radialized leaves and four appeared normal.

In addition, isolating DNA fragments using stringent hybridization conditions, does not always select for DNA fragments whose contiguous nucleotide sequence is the same or nearly the same as the probe. Fourgoux-Nicol et al (1999, Plant Molecular Biology 40 :857-872) teach the isolation of a 674bp fragment using a 497bp probe incorporating stringent hybridization conditions comprising three consecutive 30 minute rinses in 2X, 1X and 0.1X SSC with 0.1% SDS at 65⁰C (page 859, left column, 2nd paragraph). Fourgoux-Nicol et al also teach that the probe and isolated DNA fragment exhibited a number of sequence differences comprising a 99bp insertion within the probe and a single nucleotide gap, while the DNA fragment contained 2 single nucleotide gaps and together the fragments contained 27 nucleotide mismatches. Taking into account the insertions, gaps and mismatches, the longest stretch of contiguous nucleotides to

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which the probe could hybridize consisted of 93bp of DNA (page 862, Figure 2). In the present example, the isolated fragment exhibits less than 50% sequence identity with the probe.

It cannot be predicted by one of skill in the art that nucleic acids that hybridize to SEQ ID NO:1 or 3 under conditions as specified above will encode a protein with the same activity as SEQ ID NO:2 and 4. Bowie et al (1990, Science 247:1306-10, listed previously) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of the protein to fold into unique three-dimensional structures that allows it to function and carry out the instructions of the genome. The cited reference also teaches that the prediction of protein structure from sequence data and, in turn, utilizing predicted structural determinations to ascertain functional aspects of the protein, is extremely complex (pg 1306, left column). Bowie et al teach that while it is known that many amino acid substitutions are possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship, and these regions can tolerate only conservative substitutions or none at all (pg 1306, right column). The sensitivity of proteins to alterations in even a single amino acid in a sequence is exemplified by McConnell et al (2001, Nature 411 (6838):709-713, listed previously), who teach that the replacement of a glycine residue located within the START domain of either the PHABULOSA or PHAVOLUTA protein receptor with either an alanine or aspartic acid residue, alters the sterol/lipid binding domain. This change renders the protein constitutively active and therefore creates a dominant mutation which has a drastic alteration in phenotype compared to wild-type *Arabidopsis* plants.

In addition, claims 14 and 59 are not enabled for host cells "transduced" with a nucleic acid, as no viral vectors have been disclosed, or host cells transformed therewith. There is no guidance with regard to which viral vectors could be used for transformation of any or all of the cell types that are claimed.

Given the claim breadth which encompasses increasing and decreasing fruit size and/or cell division using any sequence that will hybridize to SEQ ID NO:1 or 3 in any plant species, given the unpredictability of producing a specific desired phenotype in a transformed plant; given the lack of guidance as stated above; given the breadth of the claims which encompass a multitude of sequences that have not been exemplified; given the lack of working examples of any plants with increased fruit size or of decreased fruit size in any plant species other than tomato and the lack of guidance for transforming and evaluating other sequences and plant species; it would require undue experimentation by one skilled in the art to isolate and identify a multitude of non-exemplified sequences that hybridize to either SEQ ID NO:1 or 3 from a multitude of non-exemplified plants, and to evaluate the ability of these sequences or variants thereof to cause the claimed effects in plants transformed therewith.

The enablement rejection is also maintained for the reasons of record set forth in the Official action mailed 8/6/2002. Applicant's arguments filed 2/11/2003 will be considered as they pertain to the amended claims; they have been fully considered but they are not persuasive.

Applicants contend that the amended claims enable one of skill in the art to identify useful nucleic acid molecules that hybridize to SEQ ID NO:1 or SEQ ID NO:3. Applicants recite where in the specification one skilled in the art would locate information pertinent to identifying sequences that are encompassed in the claimed invention. In particular, Applicant

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teaches that the ORFX protein is soluble, comprises an alpha/beta secondary structure, has a conserved fingerprint shared with the RAX family of proteins, and exhibits homology with twenty six plant proteins. Applicants contend that the teachings in the specification facilitate one skilled in the art to isolate via hybridization protocols or PCR, other sequences that encode proteins that regulate cell division and fruit size in plants (page 9, 1st paragraph).

The Examiner agrees that one skilled in the art could isolate nucleic acid molecules encoding other proteins based on Applicant's teachings, but the identity, and function of the encoded proteins would be a mystery. Applicant only discloses some of the basic identifying characteristics of the two proteins, SEQ ID NO:2 and 4. Applicant does not teach the particular details about the protein structure that is characteristic to proteins whose function is to regulate fruit size and cell division. Many proteins exhibit an alpha/beta secondary structure and are members of the RAX family of proteins but they do not regulate the same genes as Applicant's SEQ ID NO:1 or 3. Cell division is a complicated process involving many genes. Applicant has not specifically taught which pathway or which genes SEQ ID NO:1 or 3 regulates. Without this information, one skilled in the art could not isolate via hybridization sequences whose encoded proteins have the same function as Applicants SEQ ID NO:2 or 4.

Indefiniteness

7. Claims 5-7, 9-10, 58, 60-62, 64-65, 67-69, 70-74 and all subsequent dependent claims are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 5-7, and 9-10 "An" should be replaced with --The--.

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In claims 58, 60-62, 64-65, 67-68, 70-71, and 73-74 "A" should be replaced with --The--.

In claims 69 and 72, second line, the second "a" should be replaced with --the--.

8. Claims 5-6, and 9-10 are deemed free of the prior art, given the failure of the prior art to teach or reasonably suggest an isolated polynucleotide of SEQ ID NO:1 or 3 encoding SEQ ID NO:2 or 4, respectively.

9. No claims are allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stuart Baum whose telephone number is (703) 305-6997. The examiner can normally be reached on Monday-Friday 8:30AM – 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (703) 306-3218. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 or (703) 305-3014 for regular communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist, who may be contacted at 308-0196.

Stuart F. Baum Ph.D.

May 2, 2003


ELIZABETH F. McELWAIN
PRIMARY EXAMINER
GROUP 1800